

From the INTERNATIONAL BUREAU

PCT**NOTIFICATION OF ELECTION**

(PCT Rule 61.2)

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing:

20 August 1998 (20.08.98)

International application No.:

PCT/GB98/00461

Applicant's or agent's file reference:

11.66215/001

International filing date:

13 February 1998 (13.02.98)

Priority date:

13 February 1997 (13.02.97)

Applicant:

BLAKE, David et al

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International preliminary Examining Authority on:22 July 1998 (22.07.98)☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

ATKINSON, Peter, Birch
Marks & Clerk
Sussex House
83-85 Mosley Street
Manchester M2 3LG
ROYAUME-UNI

Date of mailing (day/month/year)

14 September 1998 (14.09.98)

Applicant's or agent's file reference

11.66215/001

IMPORTANT NOTIFICATION

International application No.

PCT/GB98/00461

International filing date (day/month/year)

13 February 1998 (13.02.98)

1. The following indications appeared on record concerning:

☒

the applicant

☒

the inventor

☐

the agent

☐

the common representative

Name and Address

ADAMS, Ged (deceased)

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒

the person

☐

the name

☐

the address

☐

the nationality

☐

the residence

Name and Address

ADAMS, Margaret (legal
representative of ADAMS, Ged,
deceased)
59 Ladder Hill
Wheatley
Oxford OX33 1HY
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

ADAMS, Ged, deceased, should be recorded as inventor only. ADAMS, Margaret, legal representative of ADAMS, Ged, deceased, should be added to the records as applicant only for the United States of America only

4. A copy of this notification has been sent to:

☒

the receiving Office

☐

the International Searching Authority

☒

the International Preliminary Examining Authority

☐

the designated Offices concerned

☒

the elected Offices concerned

☐

other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Yolaine CUSSAC

Telephone No.: (41-22) 338.83.38

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

ATKINSON, Peter, Birch
Marks & Clerk
Sussex House
83-85 Mosley Street
Manchester M2 3LG
ROYAUME-UNI

Date of mailing (day/month/year) 11 August 1998 (11.08.98)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 11.66215/001	
International application No. PCT/GB98/00461	International filing date (day/month/year) 13 February 1998 (13.02.98)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address

NAUGHTON, Declan
7 Angel Cottages
Woodhatch Road
Reigate RH2 7LJ
United Kingdom

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

NAUGHTON, Declan
Petite France Cottage
Petite France
Badminton
South Gloucestershire GL19 1AF
United Kingdom

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input checked="" type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

S. Cruz

Telephone No.: (41-22) 338.83.38

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

ATKINSON, Peter, Birch
Marks & Clerk
Sussex House
83-85 Mosley Street
Manchester M2 3LG
ROYAUME-UNI

Date of mailing (day/month/year)
11 August 1998 (11.08.98)

Applicant's or agent's file reference
11.66215/001

International application No.
PCT/GB98/00461

IMPORTANT NOTIFICATION

International filing date (day/month/year)
13 February 1998 (13.02.98)

1. The following indications appeared on record concerning:

☒ the applicant

☒ the inventor

☐ the agent

☐ the common representative

Name and Address

BLAKE, David
52 Ormonde Terrace
London NW8 7LR
United Kingdom

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person

☐ the name

☒ the address

☐ the nationality

☐ the residence

Name and Address

BLAKE, David
5 Church Street
Brill
Aylesbury
Buckinghamshire HP18 9RT
United Kingdom

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office

☐ the International Searching Authority

☒ the International Preliminary Examining Authority

☐ the designated Offices concerned

☒ the elected Offices concerned

☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

S. Cruz

Telephone No.: (41-22) 338.83.38

002177023

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

ATKINSON, Peter, Birch
Marks & Clerk
Sussex House
83-85 Mosley Street
Manchester M2 3LG
ROYAUME-UNI

Date of mailing (day/month/year) 11 August 1998 (11.08.98)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 11.66215/001	
International application No. PCT/GB98/00461	
International filing date (day/month/year) 13 February 1998 (13.02.98)	

1. The following indications appeared on record concerning:
- ☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address STRATFORD, Ian Bretton Cottage Bretton Eyam Sheffield S30 1HH United Kingdom	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:
- ☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address STRATFORD, Ian Bretton Cottage Bretton Eyam Hope Valley Derbyshire S32 5QD United Kingdom	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

- ☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Offices concerned
☒ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer S. Cruz Telephone No.: (41-22) 338.83.38
---	---

PATENT COOPERATION TREATY

PCT

19.
REC'D 20 MAY 1999

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PBA/D088187PWO		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) FOR FURTHER ACTION	
International application No. PCT/GB98/00461	International filing date (day/month/year) 13/02/1998	Priority date (day/month/year) 13/02/1997	
International Patent Classification (IPC) or national classification and IPC A61K47/48			
Applicant THERAMARK LIMITED et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 22/07/1998	Date of completion of this report 18.05.99
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Giacobbe, S Telephone No. (+49-89) 2399 8463 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB98/00461

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-39 as originally filed

Claims, No.:

2-17 as originally filed

1,18-25 as received on 16/04/1999 with letter of 15/04/1999

Drawings, sheets:

1/1 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB98/00461

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-25
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-25
Industrial applicability (IA)	Yes:	Claims	1-25 (cf Section 1.4)
	No:	Claims	

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1- Sections V and VI

1.1 Documents cited

The following documents (D) are referred to in this Report:

- D1 Chemical Abstract, 1990, vol 112(11), AN 90:91313
- D2 US 5 387 692
- D3 J. Med. Chem., 1991, 34, 2933-2935
- D4 Proceedings of the American Association for Cancer Research Annual Meeting, San Diego, CA, April 12-16, 1997, see no 2894
- D5 Anti-Cancer Drug Design, 1995, 10, 227-241
- D6 British Journal of Cancer, 1995, 72, 1462-1468
- D7 Database Dissabs, 1987, vol 49(3B), p. 745, AN 87:31004
- D8 The Merck Index, 1989, item 4369

Document D8 was not cited in the International Search Report, but was cited from the examiner's own knowledge. (cf. Section VI).

1.2 Novelty (Art 33(2) PCT)

The present application does meet the requirements of Article 33(2) PCT, because the subject-matter of claims 1-25 is new.

The available prior art does not disclose any conjugate between a therapeutic agent and a bioreductive moiety which, upon bioreduction, is broken into its components, the bioreductive moiety being transformed into a species possessing a free (claim 1) or sterically inaccessible (claim 18) alkylating centre.

1.3 Inventive Step (Art 33(3) PCT)

The present application does not meet the requirements of Article 33(3) PCT, because the subject-matter being disclosed does not involve an inventive step.

Documents D3, D4 and D7, which are considered to represent the most relevant state of the art, disclose a method for targeted drug delivery to hypoxic solid tumours based on the principle of bioreductive prodrugs. The two products of the bioreductive breakdown of the described prodrugs are the biologically active substance and a lactone (in D4 and D7) or an aminoquinoline salt (in D3). In these documents, no

mention is made of tests performed *in vivo*. The subject-matter of the present application differs in the structural features of the by-product of the bioreductive activation of the active substance, thereby supposedly resulting in a carrier which has substantially no cytotoxic activity *in vivo* (cf. page 4, line 32 to page 5, line 9 of the description). In this context, the technical problem which the present invention sought to solve may be regarded as "*how to provide a non-cytotoxic type of carrier to be used in a method for targeted drug delivery to hypoxic tissues*". However, there is no evidence in the description showing that it has actually been solved, since no comparative toxicity studies are reported. Therefore the technical problem must be reformulated as "*how to provide a different type of carrier to be used in a method for targeted drug delivery to hypoxic tissues*". The solutions proposed in the present application (cf. independent claims 1 and 18) cannot be considered as involving an inventive step (Article 33(3) PCT) because they are merely one of several straightforward possibilities from which the skilled person would have selected without the exercise of inventive skills.

1.4 Industrial applicability (Art 33(4) PCT)

For the assessment of the present claim 23 on the question of whether it is industrially applicable, no unified criteria exist in the PCT, since the patentability of claims directed to further medical uses is *inter alia* dependent upon their formulation as well as upon national and regional laws. Furthermore claims 24 and 25, which are directed to a method of treatment of the human or animal body, may not be allowable under some patent systems.

2- Section VIII

2.1 It is clear from the description on page 4, line 22 to page 5, line 9 that it is essential for the definition of the invention that the bioreductive moiety, after delivery of the therapeutic agent, either should be itself a non-toxic molecule (cf. e.g. claim 18) or should be converted into a non-toxic molecule by an internal alkylation reaction. Newly filed claim 1 however does not unconditionally contain this last feature, since the expression "*being capable of...*" is not sufficient to introduce it, given that it does not mean that the internal alkylation reaction must in any case occur. Therefore, independent claim 1 does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

2.2 The embodiment of the invention described in example 8 (cf. page 39) does not fall

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB98/00461

within the scope of the claims, since the composition contains no conjugate between a drug and a bio-reductive carrier. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).

- 47 -

20. A bio-reductive conjugate as claimed in any one of claims 1 to 17 for use in a method of targeting a therapeutic agent to a site of hypoxia and/or ischemia within the human or non-human animal body.

21. A bio-reductive conjugate as claimed in any one of claims 1 to 17 for use in the treatment of rheumatoid arthritis or other arthritic conditions, diabetes, atherosclerosis, stroke, sepsis, Alzheimer's disease and other neurological disorders, cancer, kidney disease, digestive diseases, liver disease, chronic periodontitis or ischemia following tissue transplantation.

22. Use of a bio-reductive conjugate as claimed in any one of claims 1 to 17 in the manufacture of a medicament for use as a targeting agent capable of targeting a site of hypoxia and/or ischemia within the human or non-human animal body.

23. Use as claimed in claim 21 for the treatment of rheumatoid arthritis or other arthritic conditions, diabetes, atherosclerosis, stroke, sepsis, Alzheimer's disease and other neurological disorders, cancer, kidney disease, digestive diseases, liver disease, chronic periodontitis or ischemia following tissue transplantation.

24. A method of targeting hypoxic and/or ischemic tissues in the human or non-human animal body, said method comprising administering to said body a bio-reductive conjugate as claimed in any one of claims 1 to 17.

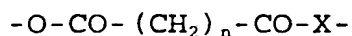
24. A method of targeting hypoxic and/or ischemic tissues in the human or non-human animal body, said method comprising administering to said body a bio-reductive conjugate as claimed in any one of claims 1 to 17.

- 46 -

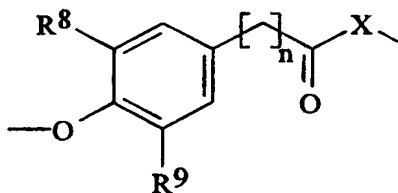
1,4-benzoquinone and the therapeutic agent is dexamethasone.

16. A bio-reductive conjugate as claimed in any preceding claim, wherein said bio-reductive moiety is linked to said therapeutic agent via a linker group L comprising an ester, phosphate ester, ether, amine, thiol or thiol ester group or any combination thereof.

17. A bio-reductive conjugate as claimed in claim 15 wherein said linker group L is a group of the formula:



or



(wherein n is an integer from 1 to 3;

X represents a sulphur or oxygen atom; and

R^8 and R^9 each independently represent F or Cl).

18. A process for the preparation of a bio-reductive conjugate as claimed in any one of claims 1 to 17, said process comprising linking at least one therapeutic agent to a non-cytotoxic bio-reductive moiety.

19. A pharmaceutical composition comprising a bio-reductive conjugate as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutical carrier or excipient.

Claims:

1. A bio-reductive conjugate comprising a non-cytotoxic bio-reductive moiety with linked thereto at least one therapeutic agent, and salts thereof.

2. A bio-reductive conjugate as claimed in claim 1 of formula I:



(where A is a non-cytotoxic bio-reductive moiety, each B is independently the residue of a therapeutic agent, and n is an integer) or a salt thereof.

3. A bio-reductive conjugate as claimed in claim 2, wherein in formula I, n is 1 to 3.

4. A bio-reductive conjugate as claimed in claim 2 or claim 3, wherein A and B are stably conjugated in an oxygenated environment and are such that following reductive activation of A, A and B detach and either A is itself a stable, non-cytotoxic species, or A reacts with itself to form a stable, non-cytotoxic species.

5. A bio-reductive conjugate as claimed in any one of claims 1 to 4, wherein said bio-reductive moiety is substantially non-mutagenic.

6. A bio-reductive conjugate as claimed in claim 1 of the formula II:

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 11.66215/001	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 98/ 00461	International filing date (day/month/year) 13/02/1998	(Earliest) Priority Date (day/month/year) 13/02/1997
Applicant THERAMARK LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (see Box I).

2. ☐ Unity of invention is lacking (see Box II).

3. ☐ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing

☐ filed with the international application.

☐ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the title, ☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

Figure No. _____ ☐ as suggested by the applicant.

☐ None of the figures.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 98/00461

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 24
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 24 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-24
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
In view of the large number of compounds which are designed by the compounds in the claims, the search was limited to the compounds mentioned in the claims or examples.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/00461

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 112, no. 11, 12 March 1990 Columbus, Ohio, US; abstract no. 91135, OELLINGER, KARIN ET AL: "Study on the redox properties of naphthazarin (5,8-dihydroxy-1,4- naphthoquinone) and its glutathionyl conjugate in biological reactions: one- and two-electron enzymic reduction" XP002052357 see abstract	1-24
Y	& ARCH. BIOCHEM. BIOPHYS. (1989), 275(2), 514-30 CODEN: ABBIA4;ISSN: 0003-9861, 1989, --- -/-	1-24



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

18 May 1998

Date of mailing of the international search report

27.05.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Berte, M

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 98/00461

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 086 068 A (RALEIGH JAMES A ET AL) 4 February 1992 see column 4, line 43 - line 58; claims 1,14,15 ---	1-24
X	US 5 387 692 A (RILEY ANTHONY L ET AL) 7 February 1995 see column 1, line 5 - column 2, line 20; claims ---	1-24
X	FIRESTONE, ALBERT ET AL: "Nitro heterocycle reduction as a paradigm for intramolecular catalysis of drug delivery to hypoxic cells" J. MED. CHEM. (1991), 34(9), 2933-5 CODEN: JMCMAR;ISSN: 0022-2623, 1991, XP002052353 see page 2933, column 2, paragraph 1 - page 2934, column 1, paragraph 2 ---	1-24
X	CHIKHALE P ET AL: "Tumor targeted prodrugs: Redox-activation of conformationally constrained, bioreductive melphalan prodrugs." EIGHTY-EIGHTH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, SAN DIEGO, CALIFORNIA, USA, APRIL 12-16, 1997. PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING 38 (0). 1997. 432-433. ISSN: 0197-016X, XP002052354 See #2894 ---	1-24
X	MEHTA, LINA K. ET AL: "Potential bioreductively activated hypoxia probes and post-irradiation radiosensitizers related to NITP" ANTI-CANCER DRUG DES. (1995), 10(3), 227-41 CODEN: ACDDEA;ISSN: 0266-9536, 1995, XP002052355 see abstract ---	1-5,9, 11,12, 16-24
X	HODGKISS R J ET AL: "Pharmacokinetics and binding of the bioreductive probe for hypoxia, NITP: effect of route of administration." BR. J. CANCER, vol. 72, 1995, pages 1462-1468, XP002052356 see abstract ---	1-5,9, 11,16-24
4 X	EP 0 659 763 A (SENJU PHARMA CO) 28 June 1995 see page 4, line 19 - line 24; claims ---	1-24
1	---	1-24

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/00461

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 25147 A (SEQUUS PHARM INC) 22 August 1996 see page 13, line 1 - line 25 ---	1-24
X	DATABASE DISSABS AN=87:31004, 1987 BERGLUND R.A.: "BIOREDUCTIVE HETEROSUBSTITUTED QUINONE ANTITUMOR DRUG DELIVERY AGENTS." XP002052358 see abstract -----	1-24

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/00461

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5086068	A	04-02-1992	NONE		
US 5387692	A	07-02-1995	US	5506345 A	09-04-1996
EP 0659763	A	28-06-1995	CA	2136803 A	23-06-1995
			JP	7228593 A	29-08-1995
			US	5599807 A	04-02-1997
WO 9625147	A	22-08-1996	AU	4981896 A	04-09-1996